At the end of the ARAC meeting, Dr. Holmes summarized the key issues/questions that were raised throughout the meeting and identified additional ones for considerations. Below is a summary of those issues that that warrant further discussion.

1. Optimal Strategies for Balancing Fixed Infrastructure Costs, Incremental Per Protocol Costs, and Variable Per Case Costs. The ratio of infrastructure costs to protocol costs has varied across networks, and for different trials. Fixed infrastructure costs include core staff, facilities, and equipment. Incremental costs per protocol include core staffing, site staffing and other incremental outlays needed to implement a protocol. Variable per case costs include tests, drugs, and other supplies. How can the RFA more explicitly optimize clinical trials productivity of the networks? Both absolute infrastructure costs, and the relative ratio of infrastructure to protocol costs can be contained by adherence to rapid timelines and teamwork assignments for efficient protocol development, clearance, and implementation; by shifting necessary core support costs from fixed infrastructure to incremental per protocol costs and to variable per case costs (to incentivize streamlined protocol adoption by network leadership and implementation later by clinical sites and to empower leadership to direct funds towards productive sites and away from non-productive sites); and by selecting sites that have already largely been developed (most of these sites will still require on-going training and development, but will require less fixed infrastructure costs than completely new sites) and therefore require less fixed infrastructure costs for site development. Incremental costs can be tightly linked to productivity (for example, by enrolling large numbers of subjects per site in a few sites, rather than small numbers per site in many sites and by enabling leadership to link contained site-funding to the site's meeting time-dependent goals for enrollment and follow-up. Variable per case costs depend on the complexity of tests required to measure primary and secondary outcomes as well as to detect adverse outcomes, as well as on the optional testing performed to pursue other scientific objectives (e.g., pathogenesis studies). Variable costs incurred by networks could be contained by shifting costs of related but optional science to other NIH peer-review mechanisms (e.g., RO1, R21, etc.).

2. Minimizing Unnecessary Redundancy in the Support Cores. What support functions could be merged across the Leadership Groups and Support Cores that compete successfully? One example could be the combining of resources across networks for training (e.g. responsible conduct of research, GCP, GLP, etc). What other functions could be integrated to flexibly serve multiple networks, as needs for particular services increase or decrease within each network over time?

3. Criteria for Evaluation. Criteria for evaluation of applications will help clarify the emphasis to be placed upon various activities of the leadership groups and the clinical sites.

4. Clinical Management Support Contract. The support contract mechanism is intended to provide very important support services that cannot be provided by the available DAIDS staff. However, effective and efficient use of this $250M contract to serve multiple protocols across networks will require technical and administrative DAIDS personnel to manage the contracts. It seems critical that DAIDS assess both the number and functional expertise of additional personnel required to adequately manage the contract.

5. Effective Partnerships at NIH. Partnerships between NIAID and other NIH IC's in clinical trial projects of mutual interest can be viewed as joint ventures, benefiting from complementary expertise, co-funding, and potentially obviating the need for various ICs establishing expensive and duplicative clinical trials infrastructure (e.g. support cores and clinical sites). The OAR could assist DAIDS and other ICs in brokering such joint ventures, and in establishing guidelines for their structure and operations. The collaboration between NICHD and DAIDS in pediatric clinical trials research appears to represent a useful model.

6. Effective Partnerships with Other Agencies. Partnerships between NIH and other US Agencies (e.g., CDC, USAID, DOD, and FDA), private foundations, and international agencies are of increasing importance, especially where international clinical research and international technical assistance in ART are rapidly expanding. Such partnerships can proactively avoid conflicts and redundancies at local, national, and international levels, while seeking synergies.

7. Role of Major Interdisciplinary Centers vs. Smaller Clinical Sites. The Draft Concept RFA would allow domestic and international sites to compete as sites for up to six different types of clinical trials. What capacities, responsibilities, level of infrastructure funding, and level o independence would characterize the major interdisciplinary sites vs. single focus sites? What is the role for small clinical sites with correspondingly small infrastructure needs that could be added to a protocol as needed to help reach enrollment targets at small additional costs? How will smaller rural primary care sites that serve most people living with HIV/AIDS in Africa become involved?

8. Clinical and Basic Science Research vs. Clinical Trials Research. If the primary mission of the clinical trials networks is to conduct clinical trials and the protocols supported by these networks also provide infrastructure to serve other clinical and basic science research, how should such research be peer-reviewed and funded?

9. Definition of "Optimizing Clinical Management." This seems to require clarification. How does this differ from RCTs of new therapeutics or new combinations of therapeutics? Should/could this be renamed "Operational and Applied Clinical Research?" Participants in ARAC and OAR meetings have repeatedly stressed the need for research that addresses locally-defined needs and priorities, especially to support scale-up of care and treatment for HIV infection internationally and in resource-poor settings.

10. Prevention Research. Within the 6 areas of clinical trials research priorities defined by DAIDS in the concept: can overlapping areas be further differentiated (e.g., therapeutics R&D through drug development and translational research vs. "optimizing clinical management"; and microbicide R&D, PMRCT, vs. prevention research? Defining "optimizing clinical management" as operational and applied clinical research on treatment, for example, would help. Examples of other prevention research (e.g., what is left after microbicides R&D, PMTCT and vaccines) could help. For example, specifying STI treatment for HIV prevention, male circumcision, use of ARVs for prevention, and prevention activities (other than ART) in the context of clinical care settings.

Note: Principles 1, 2, 3a, and 3b from the OAR working group are reiterated in points 11-15 -- some of which raise the question of how the ARAC could be used to help to review priorities and perform core support accordingly.

11. Highest Priority Science Should Drive the Structure (i.e., Infrastructure) of the NIAID Clinical Trials Endeavor, rather than Visa Versa. This is related to issue #1 above, but also has to do with establishing flexible, non-conflicted mechanisms for allocating and reallocating funding for protocols and core support within and across the networks to flexibly respond to evolving research priorities, rather than putting network leaders and DAIDS into a situation of having to justify and sustain a large, inflexible infrastructure that may not well serve certain types of studies.

12. Annual Reassessment of Scientific Priorities for Clinical Trial Research. The ARAC Working Group led by Dr. Deyton, recommended that ARAC assess DAIDS research priorities guided in part by the annual NIH AIDS research plan. This could also help in regularly defining where and how DAIDS networks could collaborate in research of interest to other ICs.

13. Regular External Evaluation of Network Progress. The French clinical trials networks undergo external review every 18 months, drawing on US expertise. Various mechanisms for periodic review of DAIDS networks could be envisioned. This could be explicitly stated in the RFA. The ARAC, supplemented by *ad hoc* members from various disciplines could be a good group to do this for several reasons – not least, the fact that as much as 2/3 of the DAIDS budget may go into these networks. This is important in any case, but especially so if funding for as long as 7 years is envisioned.

14. Objective External Review and Approval of Major (e.g., Expensive) Clinical Trials. This represents a possible role for ARAC, supplemented with additional expertise. Specific working groups could be created or panels convened to review therapeutics R&D, operational and applied clinical research, microbicide research, pMTCT, and other prevention research. The AIDS Vaccine Research Working Group could fill this role for Vaccine R&D. What is the relationship of this excellent Working Group to the ARAC? Should it have representatives at ARAC, or a more formal relationship to ARAC in the future?

15. Streamlining Protocol Development. Network restructuring can support the most efficient management of new projects from concept review, to go/no-go decisions, to implementation and completion. A plan for project management teams and evidence of ability to this could be a criterion for evaluation of competing leadership Group proposals?